Ziaka and Exadaktylos
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REVIEW

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Fluid management strategies in critically ill patients with ARDS: a narrative review

Mairi Ziaka[1*] and Aristomenis Exadaktylos[1]

Abstract

Hypervolemia is associated with worse outcomes in critically ill patients with acute respiratory distress syndrome (ARDS), with early positive fluid balance linked to longer intensive care unit (ICU) stays, prolonged ventilatory support, and increased mortality risk due to cardiopulmonary complications, lung edema, and extrapulmonary organ dysfunction. However, a restrictive fluid management strategy is associated with hypoperfusion and distal organ dysfunction, including acute renal failure and cognitive impairment. Indeed, fluid administration in patients with ARDS represents a challenge, as it must take into account the underlying condition, such as sepsis or acute brain injury (ABI), where optimal fluid management is a major determinant of disease outcome. In such cases, the approach to fluid administration should be individualized based on hemodynamic and clinical parameters according to the course of the disease. The strategy of "salvage, optimization, stabilization, and de-escalation" can guide fluid administration in the initial therapeutic approach, whereas negative fluid balance with the use of diuretics or renal replacement therapy (RRT) should be the goal once hemodynamic stabilization has been achieved.

Keywords Acute respiratory distress syndrome, Acute brain injury, Fluid management, Fluid overload, Fluid responsiveness, Sepsis

Introduction

The term ARDS refers to the acute onset of severe respiratory failure of non-cardiogenic origin, characterized by excessive hypoxemia, bilateral pulmonary infiltrates, and pulmonary inflammation with alveolocapillary hyperpermeability [1]. Since its initial description ~ 60 years ago [2] and its first definition in 1988 [3], the definition of ARDS has been re-evaluated over time. The first revision occurred in 1992 during an American–European consensus conference by the American Thoracic Society and the European Society of Intensive Care Medicine [4], followed by the ARDS Definition Task Force in Berlin in 2012 [5–7]. Recently, in light of advances in ARDS research and management, such as the use of noninvasive pulse oximetry to assess oxygenation, high-flow nasal oxygen for managing severe hypoxemic respiratory failure, and challenges in diagnosis and treatment in resource-limited settings, a revised definition has been proposed. This expanded definition includes non-intubated patients, allows the use of oxygen saturation to assess hypoxemia, and incorporates lung ultrasound as an imaging modality [8].

Fluid overload has been shown to negatively impact outcomes in ARDS patients, with early positive fluid balance during critical illness being associated with the onset of ARDS, prolonged mechanical ventilation, longer ICU stay, and an increased risk of death [9, 10]. Besides excessive inflammation, a major pathophysiological issue in the pathophysiology of ARDS is the compromised lung microvascular barrier resulting from elevated endothelial and epithelial permeability, leading to the retention of protein-rich edema fluid in both the interstitial and alveolar spaces. [11–13]. The influx of protein-rich fluid into the interstitium reduces the normal oncotic pressure

*Correspondence:
Mairi Ziaka
mairi.ziaka@gmail.com
[1] Department of Emergency Medicine, Inselspital, University Hospital, University of Bern, Bern, Switzerland

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differential between the intravascular and interstitial spaces, making ARDS patients more susceptible to the hydrostatic forces linked to elevated pulmonary capillary wedge pressure (PCWP) than those with cardiogenic pulmonary edema [14]. Recognizing that patients with ARDS are especially sensitive to hydrostatic forces related to intravascular volumes, a conservative fluid management strategy that minimizes intravenous fluid administration and includes diuretics may help lower hydrostatic pressure and increase serum oncotic pressure, potentially reducing the risk of pulmonary edema [15]. In 2007, Wiedemann et al. conducted the Fluids and Catheters Treatment Trial (FACTT), which showed that a conservative fluid management strategy for ARDS patients, guided by hemodynamic and clinical parameters, resulted to a reduced fluid balance and improved outcomes, such as improved oxygenation and an increased number of ventilator-free days [16]. A subsequent, less restrictive protocol (FACTT Lite) further supported these findings, showing similarly improved outcomes [17].

Although conservative fluid strategy is an essential aspect of ARDS management, it is also linked to detrimental effects, including the development of acute renal failure, which may require RRT [16, 18], and cognitive dysfunction [19]. In addition, it should not be overlooked that fluid management in patients with ARDS must consider its etiology, particularly in cases of sepsis or ABI, where a suboptimal fluid strategy can significantly affect the patient's prognosis [20, 21]. Indeed, extensive research highlights that mortality is lower in critically ill septic patients when appropriate fluid volumes are administered during the initial stages of resuscitation, followed by restrictive fluid management once hemodynamic stability is achieved, compared to patients who receive either insufficient or excessive fluid volumes [22]. In addition, the frequent need for positive-pressure mechanical ventilation (PPMV) in those patients underscores the critical importance of maintaining adequate cardiac preload, as sepsis commonly results in a combination of vasodilatory shock and reduced cardiac output (CO), complicating patient management [23]. Moreover, in neurocritical care patients with brain injury, hypotension and hypovolemia are associated with reduced cerebral perfusion pressure (CPP), particularly important in those with symptomatic vasospasm, acute cerebrovascular occlusions, high-grade stenoses, or impaired cerebral autoregulation, leading to exacerbation or triggering of brain injury, resulting in higher mortality and worse outcomes [24–32].

Given the complex pathophysiology of ARDS and the limited research available, this review aims to comprehensively summarize the current evidence on fluid management in patients with ARDS and to clarify resuscitation strategies for this patient population. Our work explores fluid therapy in relation to ARDS pathophysiology and examines cardio-pulmonary–renal interactions, particularly within the context of invasive mechanical ventilation (MV). It also reviews the evidence on conservative vs. liberal fluid strategies, discusses the general principles of fluid management in critical illness, including types of fluids and approaches to hemodynamic monitoring, and addresses specific clinical contexts, such as ABI and sepsis. Finally, we identify current knowledge gaps and outline potential avenues for future research.

Methods

A comprehensive literature search was conducted using PubMed to identify relevant studies focusing on fluid management in ARDS. The search terms included"acute respiratory distress syndrome,""fluid management,""fluid resuscitation,""early goal-directed therapy,""fluid responsiveness,""hemodynamic monitoring,""sepsis,""acute brain injury,"and"critical care."Boolean operators (AND, OR) and truncations were applied to refine and optimize search results. The search was focused on articles published in English over the past 20 years (2004–2024), while key seminal works predating this period were included to ensure historical context and foundational understanding. Manual screening of references from selected studies was performed to identify additional relevant literature.

Fluid management in the context of ARDS pathophysiology

Multiple factors contribute to the cumulative fluid balance in ARDS patients, especially in situations, where concurrent circulatory failure is present, characterized by low systemic vascular resistance that demands fluid resuscitation. In patients with ARDS undergoing MV, positive airway pressure significantly influences positive fluid balance. Increased airway pressure elevates intrathoracic pressure, which in turn reduces central arterial blood volume [10]. Pathological conditions can exacerbate the negative impact of PPMV on both CO and venous return, especially with the use of high levels of positive endexpiratory pressure (PEEP). In situations, where effective blood volume is decreased, whether absolutely or relatively, such as in cases of sepsis, hypovolemia, obstructive and distributive shock, and dynamic hyperinflation, it is often necessary to administer intravenous fluids to facilitate volume expansion. This approach helps to elevate mean systemic filling pressure and enhance venous return, potentially in conjunction with vasopressors and/or inotropic agents during MV [33–36]. Nevertheless, the pathophysiology of normal pressure

pulmonary edema suggests that administering fluids can elevate left atrial and pulmonary venous pressures, which may aggravate alveolar flooding and reduce arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2). Moreover, research indicates that induced hypotension, along with reduced CO and pulmonary blood flow, as seen in hemorrhagic shock, increases alveolar and physiological dead space, thereby impairing gas exchange and leading to hypercapnia [37, 38]. PPMV not only reduces ventricular preload but also elevates endogenous levels of antidiuretic hormone (ADH), renin, aldosterone, and angiotensin II, which together increase the likelihood of fluid retention and volume overload [39–41].

Hypoalbuminemia is frequently seen in inflammatory conditions and is a typical characteristic of all critically ill patients [42]. ARDS is frequently linked to hypoproteinemia, which results from hemodilution and the leakage of proteins into the interstitial and alveolar spaces, leading to decreased serum oncotic pressure that can worsen the non-cardiogenic pulmonary edema and limit diuresis [15]. Moreover, it is related to both enhanced vascular permeability, which increases the distribution volume of albumin, and a reduced half-life of albumin, ultimately resulting in a lower total albumin mass, even though there is an increase in fractional synthesis [43].

Cardio-pulmonary–renal interactions in ARDS and invasive mechanical ventilation

Acute kidney injury (AKI) affects approximately one-third of mechanically ventilated patients and is associated with worse short- and long-term outcomes, as well as high mortality [44–46]. The pathophysiology of AKI in mechanically ventilated patients is multifactorial, including MV-associated hemodynamic alterations impairing venous return and CO, neurohormonal pathways, inflammatory cascades associated with lung injury (LI) and MV, and gas exchange disturbances, such as hypoxemia and hypercapnia (Fig. 1) [47–49].

PPMV fundamentally differs from the physiology of spontaneous ventilation, where positive intrathoracic pressures occur only transiently, particularly during coughing or the Valsalva maneuver [50]. PPMV is associated with significant hemodynamic consequences,

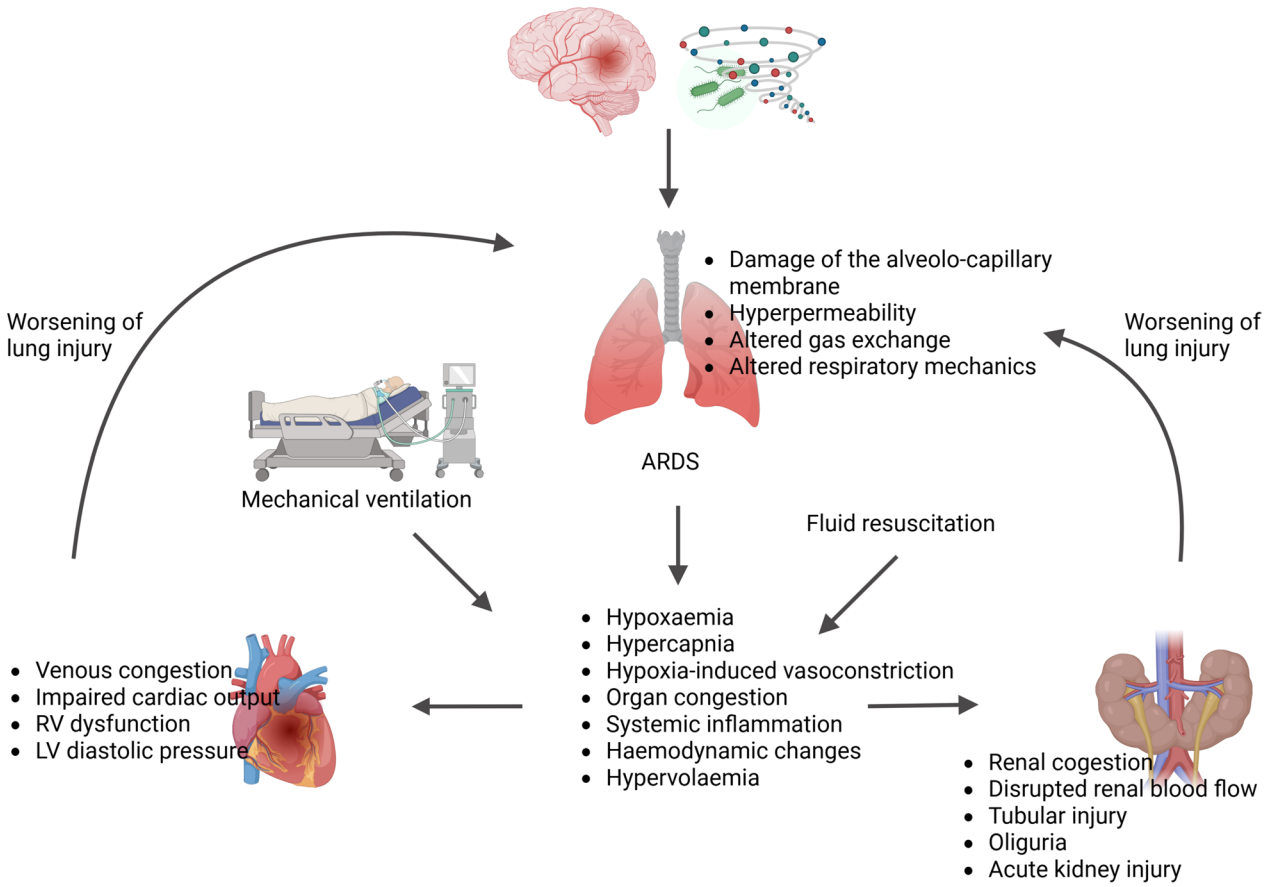

Fig. 1 Cardio-pulmonary–renal interactions in ARDS and invasive mechanical ventilation. *ARDS* acute respiratory distress syndrome, *LV* left ventricle, *RV* right ventricle

including increased right atrial pressures due to elevated intrathoracic pressures, which subsequently reduce the pressure gradient for venous return. As a result, altered venous return leads to decreased right ventricular (RV) preload and impaired organ perfusion. In addition, increased pulmonary vascular resistance may further impact RV stroke work, while a reduced intrathoracic-to-extrathoracic aortic pressure gradient lowers left ventricle (LV) afterload and stroke work, ultimately leading to a decrease in CO proportional to mean airway pressure (Fig. 1) [51, 52]. In the kidneys, elevated intrathoracic pressures, impaired CO due to impeded venous return, and atrial stretch lead to MV-related reductions in renal blood flow [53]. Moreover, elevated intrathoracic pressures and compromised RV function contribute to increased renal congestion due to reduced venous return, which manifests as elevated central venous pressure (CVP) and pulmonary vascular resistance [48, 54]. In addition, PEEP levels—a key component of the ventilatory strategy in patients with ARDS—are an additional factor leading to increased intra-abdominal pressure, depending on the level of positive pressure, respiratory system elastance, and pre-existing abdominal pressure. In combination with the caudal movement of the diaphragm, this may further worsen venous congestion and impair renal perfusion [44, 55, 56]. On the other hand, critically ill patients with AKI are at a significantly higher risk of developing severe respiratory failure requiring MV [57, 58].

Even with contradictory results, research highlights that PPMV may activate neurohormonal mechanisms influencing renal function, including the renin–angiotensin axis, secretion of ADH, atrial natriuretic peptide (ANP) production, and sympathetic activation. ADH secretion leads to a redistribution of intrarenal blood flow from the cortex to the medulla, resulting in prerenal vasoconstriction and greater fluid retention at any level of renal perfusion [59–62]. Moreover, the secretion of ADH can occur in response to PEEP [63], further exacerbating fluid retention and hypervolemia. Although the underlying pathophysiologic mechanisms behind this paradoxical effect are not fully understood, it is hypothesized that multiple factors contribute, including arterial baroreceptor activity [64, 65]. Furthermore, clinical and experimental research has shown that sympathetic activity related to PPMV is associated with increased renin activity, stimulation of the renin–angiotensin axis, impaired renal function, fluid and salt retention, and oliguria [40, 48, 63, 65–67]. In contrast, atrial and cerebral natriuretic peptides counteract these effects by promoting natriuresis through the direct inhibition of renin secretion from juxtaglomerular cells and the suppression of aldosterone production and release [63, 68, 69].

Although MV is a life-saving intervention for patients with ARDS, it can also aggravate LI, a phenomenon known as ventilator-induced lung injury (VILI) [70]. The pathophysiology of VILI is complex and involves multiple mechanisms, including increased trans-alveolar (transpulmonary) pressures (barotrauma), alveolar distension (volutrauma), and cyclic alveolar opening and closure (atelectrauma). In addition to structural consequences, these mechanical forces activate complex inflammatory pathways, triggering regional and systemic inflammatory responses (biotrauma) that can extend to extrapulmonary organs, including the kidneys [7, 71]. MV-associated inflammatory cascades can spread through the systemic circulation due to increased alveolar–vascular permeability, leading to the decompartmentalization of the inflammatory response and affecting extrapulmonary organs and systems [7, 72]. These inflammatory mediators include tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, soluble TNF-α receptor 75, IL-1β, and IL-1 receptor antagonist (IL-1ra), detected in both plasma and bronchoalveolar lavage fluid of mechanically ventilated patients, as well as in experimental models of MV [73–76]. Among these mediators, some have been implicated in kidney injury by inducing epithelial cell apoptosis and reducing renal blood flow, with these effects being more pronounced in individuals who received lung-injurious MV [49, 77].

Arterial blood gas abnormalities, such as systemic acidosis, hypoxemia, and hypercapnia, may impact renal function and contribute to AKI by reducing renal perfusion pressure and altering renal vascular resistance (Fig. 1). These effects occur through various pathogenic mechanisms, including adrenergic stimulation and disruptions in nitric oxide metabolism [48, 78]. Although it is well-established that lung-protective ventilation with low tidal volumes (6 mL/kg) and PEEP improves prognosis in patients with ARDS, it may also lead to hypercapnia and acidemia [79]. Indeed, a retrospective cohort study of ARDS patients with normal renal function prior to ARDS onset highlighted that acidosis on day 1 was significantly related to the occurrence and severity of AKI [80] and is associated with elevated oxygen consumption in the proximal tubule [81, 82]. Moreover, hypercapnia may promote vasoconstriction of the renal vasculature, resulting in elevated vascular resistance, decreased renal blood flow (RBF) and glomerular filtration rate (GFR), and reduced natriuresis [48, 83]. Finally, in patients with severe LI, hypoxia-related renal ischemia with PaO_2 levels below 75 mmHg contributes to an imbalance between renal oxygen supply and demand, the formation of harmful metabolic byproducts, necrosis of tubular epithelial cells, and impairment of renal function [84].

Conservative vs. liberal fluid strategies

A fluid administration strategy in critically ill patients is a real challenge in daily clinical practice, given the need to achieve adequate oxygen delivery and tissue perfusion while reducing the development or worsening of potential LI [85]. An unrestricted fluid administration strategy during the initial resuscitation phase is referred to as liberal and is also characterized by the absence of targeted fluid removal after the patient achieves hemodynamic stabilization. The rationale behind this approach is that increasing stroke volume can improve end-organ perfusion and enhance oxygen delivery [86]. About 40 years ago, observational studies found that liberal fluid strategies were linked to poorer clinical outcomes in ARDS patients [87]. Indeed, early in critical illness, a positive fluid balance significantly increases the risk of developing ARDS and contributes to higher mortality rates. In addition, despite careful monitoring, the majority of ARDS patients present with a positive fluid balance at onset, which not only exacerbates LI but also predicts prolonged MV, extended ICU and hospital stays, and an overall increase in mortality [9, 88, 89]. Moreover, hypervolemia is linked to organ failure and is identified as an independent predictor of adverse outcomes in critically ill patients [90–93]. The clinical effects of hypervolemia are particularly evident in lung function, where respiratory failure becomes apparent early. However, fluid overload can also impact other organs and systems, such as the kidneys, which, being encapsulated organs, are especially prone to developing AKI. Additional complications include delirium, abdominal compartment syndrome, and impaired wound healing [94–97]. Furthermore, it should be kept in mind that the interaction between fluid administration and MV strategies may contribute to VILI, potentially aggravating the damage. For example, in experimental models of LI, combining a high volume of fluids with pressure–support ventilation, rather than pressure control ventilation, has been associated with worse LI. Furthermore, it has been highlighted that endothelial damage in the lungs is aggravated when a large volume of fluid is administered, especially with the use of high PEEP or a sudden reduction in PEEP [98].

In general, hypervolemia results in tissue and interstitial edema, hinders blood flow and lymphatic flow, impairs metabolism, alters oxygen diffusion, and disrupts cell-to-cell interactions [99, 100]. While the pathophysiologic mechanisms of delirium in critically ill patients are multifactorial, its association with fluid overload has become increasingly recognized in recent years [101, 102]. Moreover, based on observations in patients with cardiorenal and cardiohepatic syndromes, it has been suggested that increased venous pressures and venous congestion, leading to edema formation, organ structure compression, and altered brain perfusion, may represent potential pathophysiologic mechanisms of neurocognitive impairment in patients with fluid overload [103]. Further complicating the issue, it could be hypothesized that the detrimental effects of hypervolemia on brain function are more pronounced in patients with blood–brain barrier (BBB) dysfunction, such as those with ABI, ARDS, and sepsis, due to increased fluid passage into the brain [104–107]. Recently, it has been suggested that the combination of increased intrathoracic pressure during controlled MV and potential meningeal lymphatic congestion, resulting from ineffective suction due to insufficient negative pleural pressure, may play a role in the pathogenesis of ICU delirium [108].

Emerging evidence points to the potential for improved outcomes with the use of restrictive fluid strategies, including diuresis, particularly among patients facing critical illness and ARDS [109–114], which are associated with a lower requirement for invasive MV, diminished organ dysfunction, and a trend toward reduced dependence on RRT [16, 112]. Unlike liberal fluid management, a conservative approach restricts resuscitation fluids and reduces fluid accumulation to mitigate pulmonary edema and enhance ventilation–perfusion balance, albeit with a potential risk of impaired cardiac perfusion and end-organ injury [86]. A historical study involving 1000 patients with LI compared liberal fluid administration with conservative administration based on hemodynamic and clinical parameters, such as shock, oliguria, and compromised circulation. The authors concluded that the restrictive fluid strategy resulted in significantly lower fluid accumulation and highlighted improvements in the oxygenation index, ventilator-free days, and lung injury scores. Moreover, the 60-day mortality, incidence of shock, vasopressor use, and dialysis rate did not differ between groups, indicating the safety of the restrictive fluid strategy [16]. These findings are further supported by previous research in mechanically ventilated ICU patients, highlighting positive fluid balance as an independent risk factor for ARDS progression [85].

Diuretics are frequently used in critically ill patients, including those with ARDS, and have demonstrated benefits in improving patient outcomes. Although the impact on mortality remains inconclusive, several studies have shown that diuretics can effectively reduce positive fluid balance, improve lung function, and shorten the duration of MV. These positive effects suggest that diuretics play a valuable role in managing ARDS, even though their direct impact on mortality has yet to be definitively established [16, 115]. In patients with ARDS and AKI, positive fluid balance may increase mortality, whereas proper use of furosemide could help resolve kidney injury and improve outcomes [116, 117]. Seitz et al.

performed a retrospective multicenter cohort study to investigate fluid management in ARDS patients, demonstrating that early diuretic use (48–72 h after ARDS onset) was associated with lower hospital mortality and lower crystalloid fluid intake during the first 48 h, which reduced hospital mortality [118]. A secondary analysis of the ARDS Network FACTT trial evaluated the effect of diuretics on 28-day mortality in ARDS patients without early RRT. Using a marginal structural Cox model, diuretics were associated with reduced mortality. Latent class analysis identified benefits in patients with worse renal function and higher CVP, while subgroup analysis showed advantages in females, sepsis-induced ARDS, $PaO_2/FiO_2 \leq$ 150 mmHg, and mean arterial pressure (MAP) $\geq$65 mmHg [119]. Moreover, an additional secondary analysis of the FACTT trial identified two ARDS subphenotypes, consistent with prior findings, with subphenotype 2 characterized by elevated inflammatory markers and hypotension. Mortality outcomes varied significantly between the subphenotypes based on fluid management strategies; while a fluid-conservative strategy reduced mortality in subphenotype 2, it increased mortality in subphenotype 1. These results underscore the existence of biologically distinct ARDS subphenotypes with distinct responses to fluid strategies, highlighting the need for personalized treatment approaches [120]; however, these results remain unconfirmed by prospective validation.

Using the GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluations), the Faculty of Intensive Care Medicine and Intensive Care Society Guideline Development Group (2019) has made recommendations for managing adult patients with ARDS. While the evidence for most outcomes is of low quality, primarily influenced by a single trial, conservative fluid management appears to provide benefits without causing harm. Based on these findings, it is advised that clinicians consider a conservative fluid strategy for ARDS patients, which involves fluid restriction, diuretics, and possibly hyperoncotic albumin, to maintain a neutral or negative fluid balance [121].

Fluid management in critical illness

Concerns persist that adopting a conservative fluid management strategy in critically ill patients could increase the risk of non-pulmonary organ failures, particularly in the form of shock and AKI [86]. Immediate fluid resuscitation is typically necessary in clinical situations such as hypovolemic shock resulting from hemorrhage due to trauma or major surgical procedures, or from extravascular fluid loss associated with systemic inflammatory responses, as observed in cases of sepsis or burns [122]. Fluid requirements for patients cannot be determined using a one-size-fits-all formula; instead, they must be tailored to the patient's needs and guided by hemodynamic monitoring. The timing of fluid administration is equally crucial and varies across the different resuscitation phases, including salvage, optimization, stabilization, and de-escalation (Fig. 2) [97, 123]. The concept of early goal-directed therapy (EGDT) has been developed with the goal of reversing sepsis-induced hypoperfusion by maintaining a CVP of 8–12 mmHg through intravenous fluid boluses, supporting MAP between 65 and 90 mmHg with vasopressors, and achieving a central venous oxygen saturation ($ScvO_2$) greater than 70%. This is done through the use of inotropes and/or red blood cell transfusions [124–128]. Moreover, the 1-h bundle guidelines for septic patients emphasize the importance of administering crystalloids quickly and early in the initial resuscitation phase. This approach is recommended for patients with either arterial hypotension or elevated blood lactate levels (above 4 mmol/L) to help restore adequate perfusion pressure [10]. Although the appropriate volume of fluid required for effective resuscitation in septic patients remains a topic of ongoing debate, most clinical studies in adults presenting to an emergency department with sepsis or septic shock adopt a fluid administration strategy of 30 mL/kg within the first 3 h of sepsis onset, which has been associated with lower in-hospital mortality, shorter ICU stays, and improved hemodynamic response, regardless of comorbidities, such as heart failure or end-stage kidney disease [127, 129, 130]. The early administration of norepinephrine should be considered, as it has been shown to positively impact cumulative fluid balance, according to a propensity-score matched analysis of 337 patients allocated to either a very early vasopressor group (< 1 h) or a delayed vasopressor group [131]. This approach is particularly important in patients with severe hypotension, as vasopressor therapy should be initiated alongside fluid administration due to the clear relationship between the magnitude and duration of hypotension and patient outcomes. In addition, in septic shock, hypotension is largely caused by vasoplegia, which cannot be corrected by fluid administration alone [132–134]. However, although existing evidence on managing patients with ARDS and circulatory failure is limited, the sub-phenotype of ARDS should be considered, as its heterogeneous nature can influence patient responses to fluid management [135]. As mentioned above, the hypo-inflammatory sub-phenotype could benefit from more liberal fluid administration, whereas the hyper-inflammatory sub-phenotype does not [120].

During the optimization phase, fluid administration should be tailored to individual needs, considering the clinical context, and guided by indices that help assess the risk of excessive fluid administration [136, 137]. To

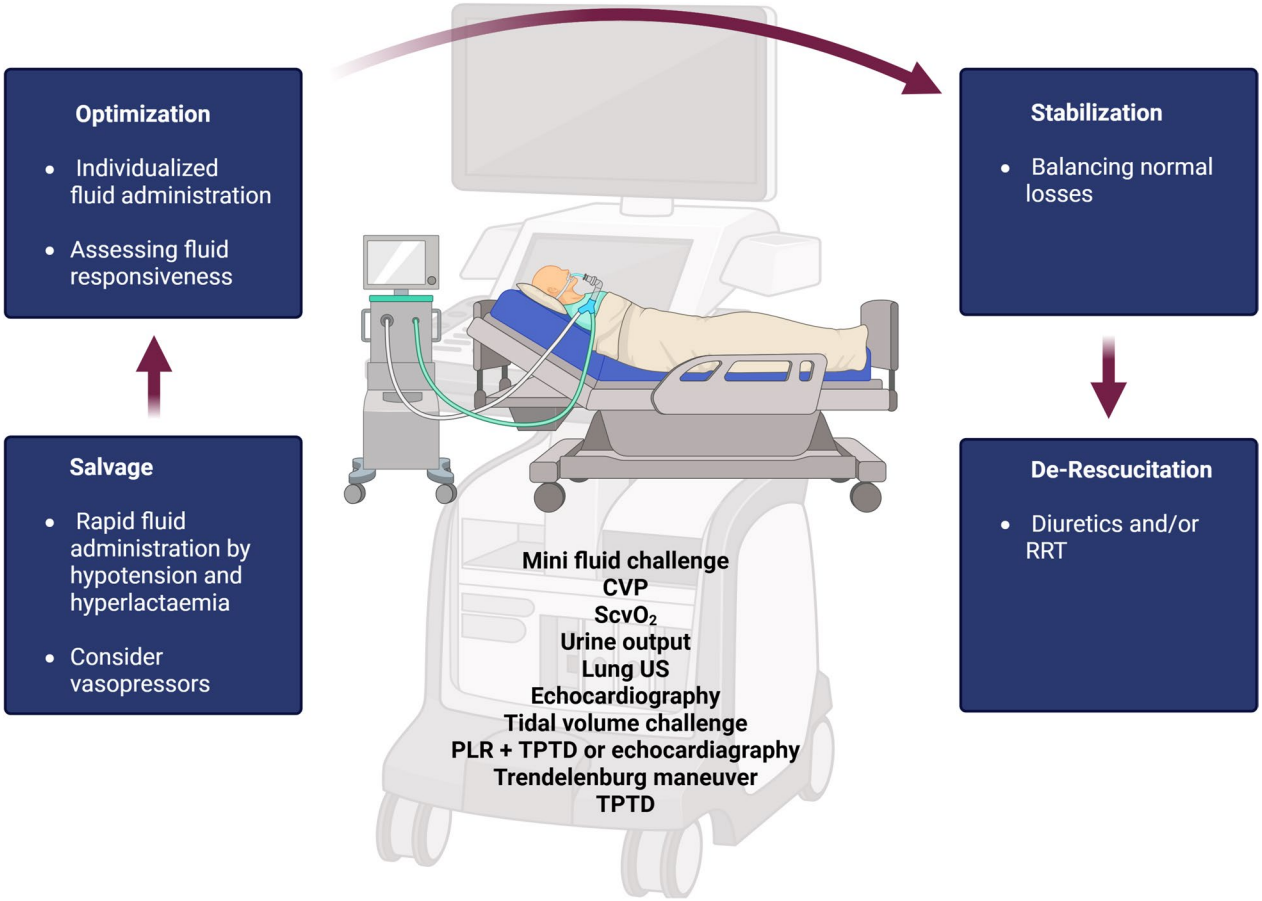

Fig. 2 Four phases of fluid resuscitation and available hemodynamic monitoring modalities in critically ill patients. *CVP* central venous pressure, *PLR* passive leg raising, *RRT* renal replacement therapy, *$ScvO_2$* central venous oxygen saturation, *TPTD* transpulmonary thermodilution, *US* ultrasound

guide adequate therapy, potential targets for personalized fluid management strategies include repeated lactate measurements, as well as clinical assessments, such as echocardiography, $ScvO_2$, invasive hemodynamic monitoring, or evaluation of capillary refill time [138]. Moreover, during this stage of fluid management, intravenous fluids are administered in carefully measured amounts, with close monitoring of the patient's response (Fig. 2). To ensure fluids are provided only to those who will benefit, it is essential to evaluate indicators of fluid responsiveness, such as pulse pressure variation (PPV), stroke volume variation (SVV), and the passive leg raising (PLR) test, before administering additional doses [97, 139]. Furthermore, fluid responsiveness can be determined using the fluid challenge test, which delivers a fixed volume of fluids to identify patients likely to increase CO and enables individualized fluid titration while minimizing hypervolemia and fluid accumulation [140]. In research on fluid challenge and fluid responsiveness, a median volume of 500 mL is commonly used, which aligns with the median volume used in the FENICE study, while smaller volumes are often employed in high-risk surgical patients receiving goal-directed therapy for optimization [141–143]. However, identifying fluid responsiveness in a patient does not necessarily indicate a need for fluid loading, as the primary objective of resuscitation is to enhance oxygen delivery and tissue perfusion to meet the body's metabolic demands, rather than simply normalizing a dynamic fluid responsiveness index [144].

In patients in the prone position, the assessment of fluid responsiveness becomes more individualized, as the hemodynamic and respiratory changes associated with it [145] can significantly influence fluid responsiveness. The determination of dynamic parameters, such as PLR, PPV, and end-expiratory occlusion (EEO), which are primarily used to assess fluid responsiveness in mechanically ventilated patients, has some limitations in patients in the prone position under MV [146]. In the prone position, the PLR test is obviously unreliable [147]. In addition, it should be used with caution in patients with ABI, as it can lead to increases in ICP and impair cerebral autoregulation [148]. However, a prospective

study including ARDS patients in the prone position with acute circulatory failure highlighted that changes in cardiac index during a Trendelenburg maneuver can be used to predict fluid responsiveness in these patients (Fig. 2) [149]. Recently, although still a topic of discussion, it has been proposed that the limitation of performing the PPV test due to low tidal volumes during protective ventilation could be minimized using the tidal volume challenge [146, 150, 151]. Importantly, this method has been shown to be acceptable for predicting fluid responsiveness during elective neurosurgical operations, in contrast to PPV and EEO [152]; nevertheless, the data are very limited and should be further validated, especially in the context of ABI.

During the stabilization phase, fluid therapy should be limited to maintaining normal fluid losses (such as renal, gastrointestinal, and insensible losses) and replacing fluids if the patient continues to experience losses due to ongoing pathological conditions [113, 153]. In this stage, neither shock (compensated or uncompensated) nor an approaching threat of shock is present, setting it apart from the previous two stages [153]. In the final stage, known as the de-escalation phase, the patient has stabilized, and fluid administration is minimized. The main objective is to eliminate excess fluids and achieve a negative fluid balance, either spontaneously or with the help of diuretics. Loop diuretics, such as furosemide, are commonly used in clinical practice but can be associated with adverse effects, including hypernatremia. As a result, careful management of fluids and electrolytes is crucial to prevent complications, making vigilant monitoring and timely adjustments essential to support the patient's recovery effectively [97, 154].

Types of resuscitation fluids

Colloids vs. crystalloids

The major types of resuscitation fluids can be divided into two main categories: crystalloids, including isotonic saline and balanced solutions, and colloids, with albumin as the principal representative [155]. Due to their larger molecular weight, colloids demonstrate prolonged intravascular persistence. Consequently, the combined use of colloids and crystalloids may reduce the total volume of fluids required, thereby lowering the risk of hypervolemia and edema [97, 156]. The CRISTAL trial, a randomized clinical trial including a mixed ICU population (sepsis, trauma, or hypovolemic shock without sepsis or trauma), investigated the effects of colloids vs. crystalloids in patients with hypovolemic shock. The study found that while 28-day mortality did not differ between groups, 90-day mortality was significantly lower in the colloid group. Moreover, patients who received colloids had more days alive without MV than those in the crystalloid group, at both 7 and 28 days. Similarly, they had more days alive without vasopressor therapy at these timepoints [157]. In the intraoperative setting, Joosten et al. demonstrated that patients receiving a combination of colloids and crystalloids required significantly less intraoperative fluid and experienced fewer postoperative complications [158]. These findings are consistent with a meta-analysis comparing colloids and crystalloids across different patient populations, which showed that larger volumes of crystalloids were required to achieve the same hemodynamic targets [159]. However, the SAFE trial, a double-blind randomized controlled trial conducted in critically ill ICU patients, compared 4% human albumin solution (HAS) to normal saline. The volume of albumin to saline varied from 1:1.2 to 1:1.6, and outcomes at 28 days were comparable between the two groups [99]. Recently, the ABC-sepsis trial, an open-label, parallel-group randomized feasibility trial, compared balanced crystalloids with 5% HAS for fluid resuscitation in septic patients during the first 6 h following randomization and found lower mortality in the balanced crystalloids group [160]. Moreover, the SAFE–TBI trial highlighted higher mortality rates in neurocritically ill patients with traumatic brain injury (TBI) who received 4% albumin compared to those who received isotonic saline [21]. Nonetheless, in contrast to the SAFE and the ABC-sepsis trial, a recent meta-analysis evaluating the efficacy of albumin vs. crystalloids for fluid resuscitation in septic patients found that treatment with 20% HAS significantly improved 90-day mortality in patients with septic shock, raising the question of whether the concentration of albumin solution should be a factor to consider [161]. Nevertheless, the mortality benefit observed in septic shock patients treated with albumin could be attributed not only to its hemodynamic effects but also to other properties, such as its antioxidant effects and drug-carrying ability [97].

Research data on the use of albumin vs. crystalloids in patients with ARDS is limited. In a subgroup analysis of the SAFE trial in patients with ARDS, the relative risk of death was slightly lower in those who received albumin compared to those who received crystalloids, although this difference did not reach statistical significance [99]. A small prospective study investigating the effects of colloids vs. crystalloids in patients with severe respiratory failure showed that in those who received albumin, the pulmonary shunt at the end of the study was significantly lower, but without influencing the outcome. Moreover, patients in the crystalloid group received greater amounts of fluids compared to the albumin group, though the difference was not statistically significant [162]. Moreover, van der Heijden et al. demonstrated in septic and non-septic mechanically ventilated patients

with clinical hypovolemia that the severity of pulmonary edema and LI score did not differ significantly between patients who received colloids, including albumin, and those who received crystalloids. Nevertheless, this study also highlighted statistically significant increases in plasma volume, cardiac index, and CVP with the use of colloids, whereas the volume administered was significantly higher in the crystalloid group [163]. Based on the populations from the three aforementioned studies, an international panel of clinical experts and methodologists conducted a pooled analysis comparing albumin with crystalloids in patients with severe acute respiratory failure and found that the use of albumin had no effect on mortality, although the evidence was very uncertain. Considering the very low certainty of the evidence and the disadvantageous factors associated with albumin use, such as higher costs, availability, limited resources, patient preferences, and rare allergic reactions, the European Society of Intensive Care Medicine (ESICM) recently recommended the use of crystalloids rather than albumin in patients with severe respiratory failure, sepsis, and ABI [164].

Balanced crystalloids vs. isotonic saline

The administration of crystalloids is a very common intervention in critical care, with isotonic saline (0.9% saline) being the most widely used resuscitation fluid worldwide [155]. However, the use of chloride-rich intravenous fluids, such as normal saline, has been associated with an increased risk of AKI [165, 166]. Indeed, the administration of large amounts of normal saline is linked to the development of hyperchloremia and hyperchloremic metabolic acidosis, which can impair renal function, disrupt coagulation, and potentially increase mortality [167–170]. Furthermore, significant elevations in chloride concentrations have been associated with hypotension, renal vasoconstriction, altered immune and inflammatory responses, and impaired microcirculation [166].

Balanced crystalloids such as Ringer's lactate and plasmalyte A (Baxter Inc.) have chloride concentrations more similar to plasma compared to normal saline, as they substitute a portion of chloride with organic anions, such as lactate and acetate, thereby reducing the risk of hyperchloremic metabolic acidosis [155, 171]. Based on the findings that the use of balanced crystalloids could lead to improved outcomes, a growing use of these fluids has been observed in recent years [172]. A secondary analysis of the SMART (Isotonic Solutions and Major Adverse Renal Events Trial), including critically ill adult septic patients, revealed that the use of balanced crystalloids was associated with a lower 30-day in-hospital mortality, a lower incidence of major adverse kidney events within 30 days, and a greater number of vasopressor-free days and RRT-free days compared with the use of saline [166]. These findings align with the results of previous studies showing that septic patients who received balanced salt solutions, compared to isotonic solutions, had decreased rates of AKI [165] and a lower risk of in-hospital mortality [173]. However, a systematic review and meta-analysis of 13 randomized controlled trials, including 35,884 critically ill patients, found no statistically significant difference in 90-day mortality between those who received balanced crystalloids and those who received isotonic saline. In addition, in studies with low risk of bias, there were also no significant differences in secondary outcomes, including the incidence of AKI, new treatment with RRT, and ventilator-free and vasopressor-free days by day 28 [174].

Fluid osmolarity is a key concern in patients with ABI, as free water may passively move through the BBB, resulting in an increase in brain water content and cerebral edema in response to an acute decrease in plasma osmolarity [175, 176]. Indeed, previous research highlights an increased mortality among patients with TBI who received balanced crystalloids compared to normal saline [177–179]. A recent additional subanalysis of the SMART trial, including neurocritically ill patients with TBI, reported a worse discharge disposition in those who received balanced salt solutions compared to saline, whereas a clinically relevant increase in mortality could not be excluded [180]. Based on current evidence, recent guidelines for fluid management in critically ill patients recommend the use of isotonic saline over balanced crystalloids for fluid resuscitation in adult patients with TBI. In addition, considering observational data that show harmful effects of Ringer's lactate administration in TBI patients, and given that most studies in neurocritical care patients used near-isotonic balanced crystalloids, experts recommend against the use of Ringer's lactate (or acetate) in those patients [164].

Hemodynamic monitoring in critical illness

The undeniable value of advanced hemodynamic monitoring in managing critically ill patients with severe shock is well-established and strongly recommended by guidelines from Intensive Care Medicine societies [181]. Despite the usefulness of CVP being questioned in various studies, CVP remains a widely used hemodynamic parameter to guide fluid management in critically ill patients (Fig. 2) [182–187]. Although there are significant limitations to the use of CVP in assessing cardiocirculatory status, CVP is suggested to potentially contribute to the management of patients with shock, provided its pathophysiological limitations are understood [188]. Indeed, extreme values of CVP can

be helpful in determining fluid responsiveness, with low values indicating a hypo- or normovolemic status that may benefit from fluid administration, and high values suggesting a normo- to hypervolemic status or RV failure, in which volume administration could have deleterious effects [182, 189]. Notably, values of 8–12 mmHg could represent useful thresholds, as most patients with CVP values below 8 mmHg are volume responders, while only a minority of patients with values above 12 mmHg will respond to fluid administration [189, 190]. However, fluid resuscitation guided by a single CVP measurement should be avoided, as baseline CVP has been shown not to differ between responders and non-responders [182].

The transpulmonary thermodilution (TPTD) method is an advanced hemodynamic monitoring technique that can be considered minimally invasive, as it requires only the insertion of a central venous catheter and an arterial thermistor catheter, allowing measurements of CO, which is a cornerstone in the management of shock as it reflects oxygen delivery to the tissues (Fig. 2) [123, 191]. Moreover, determination of CO may aid in differentiating the type of shock, as it is routinely low in hypovolemic and cardiogenic shock and high in septic shock, particularly following fluid resuscitation [123]. Beyond CO measurements, TPTD allows the holistic evaluation of hemodynamic status by estimating volumes and pressures, such as PPV and SVV to guide fluid management, ejection fraction to evaluate LV function, extravascular lung water (EVLW) to assess lung permeability and pulmonary edema, and global end-diastolic volume to reflect cardiac preload [192, 193]. Despite the questionable survival benefit of advanced hemodynamic monitoring in critically ill patients, the assessment of EVLW and pulmonary vascular permeability remains a key variable in the management of ARDS, as they predict outcomes and mirror the severity of alveolar damage, respectively, while also guiding fluid therapy [194–197]. Furthermore, clinical research highlights the prognostic accuracy of EVLW in assessing positive fluid balance and mortality after initial fluid resuscitation in septic patients [198]. In addition, studies have demonstrated that in patients with sepsis-induced LI, EVLW and permeability indexes are significantly elevated in nonsurvivors, suggesting that these parameters may serve as indicators of prognosis and severity [199]. These data are further supported by experimental research showing a strong correlation between the pulmonary vascular permeability index and the severity of septic ARDS [200].

For patients with ABI, a task force of the European Society of Intensive Care Medicine recommends the use of advanced hemodynamic monitoring to evaluate hemodynamic status and assess volume responsiveness to prevent or minimize secondary brain injury [181]. Indeed, accumulating research demonstrates that TPTD-directed fluid management in patients with subarachnoid hemorrhage results in a decreased incidence of delayed cerebral ischemia and improved systemic hemodynamics [201–203]. However, clinical approaches to hemodynamic evaluation in neurocritically ill patients vary across centers and are primarily used for those with severe damage. Nonetheless, hemodynamically stable patients may also benefit from advanced monitoring, such as TPTD [204].

Lung ultrasound has become an important tool in managing critically ill patients, including those with ARDS [205, 206]. Typical findings of ARDS on lung ultrasound include signs of aeration loss, such as bilateral B-lines and consolidations. Sonographic differentiation from cardiogenic interstitial edema can be performed by assessing heterogeneous aeration loss with spared lung regions, pleural irregularities, and subpleural consolidations [207, 208]. Moreover, combining lung ultrasound findings related to pulmonary edema with critical care echocardiography, including the evaluation of dynamic variables, such as flow velocity and velocity–time integral, can help assess fluid responsiveness through repeated bedside measurements [209–212].

The promising potential of predictive technologies with machine-learning algorithms with real-time data analysis, such as the Assisted Fluid Management (AFM) software and the Acumen Hypotension Prediction Index (HPI), to early recognize hemodynamic instability at the bedside, predict fluid responsiveness, and guide interventions, will further contribute to the optimization of hemodynamic monitoring in these complex ICU patients [213–217].

Fluid management in patients with ARDS and acute brain injury

Besides damage or dysregulation of the respiratory center, ABI is often associated with various forms of LI, including neurogenic pulmonary edema, lung inflammation, ARDS, aspiration pneumonia, and ventilator-associated pneumonia (VAP) [218–220]. LI/ARDS is commonly observed in patients with ABI, with reported incidence rates ranging from 5 to 30%, depending on the type of brain injury [106]. Although a restrictive fluid management approach and intensive diuretic therapy are frequently advised for ARDS [16], maintaining euvolemia remains essential to support adequate CPP in patients with ABI (Fig. 3) [221]. Indeed, a decrease in CPP caused by hypotension can result in cerebral vasodilation, which worsens intracranial hypertension [222], which is a crucial aspect of managing ABI [223]. Moreover, it is important to keep in mind that in patients with ABI, hemodynamic instability can arise from shock related to the brain injury, which is marked

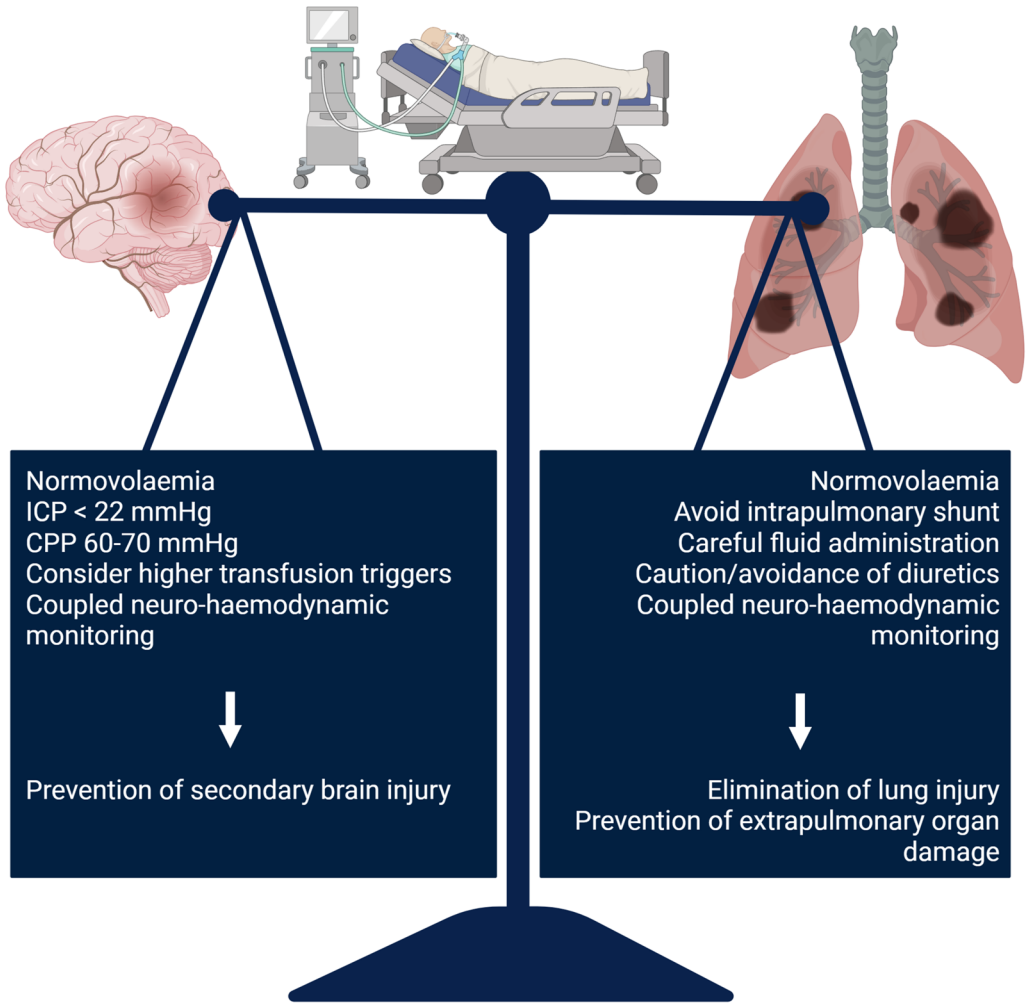

Fig. 3 Main goals of fluid resuscitation therapy in critically ill patients with concomitant ARDS and ABI. *CPP* cerebral perfusion pressure, *ICP* intracranial pressure

by a surge of catecholamines that contributes to ventricular dysfunction and vasoplegia [224]. In addition, dehydration raises the risk of acute renal failure, further complicating the management of patients with ABI [225]. In a study of 392 patients aged 16–65 with severe, non-penetrating brain injuries and Glasgow Coma Scale scores of 3–8 after resuscitation, researchers assessed the effects of moderate hypothermia. Their findings revealed that a fluid balance below − 594 mL was associated with poorer outcomes, showing a negative impact that was independent of intracranial pressure, mean arterial pressure, or CPP, underscoring the significance of optimal fluid management in improving outcomes for severely injured neurocritical ill patients [226]. Given the complex interactions between these factors, precise regulation of hemodynamics and fluid balance is essential for reducing secondary injuries and promoting optimal recovery (Fig. 3) [227].

Conversely, hypervolemia can have detrimental effects on patients with ABI. Indeed, fluid overload can exacerbate cerebral edema in patients with BBB disruption, enhance the risk of heart failure, cardiogenic shock, and pulmonary edema, and is associated with higher ICU mortality and worse outcomes in ABI [228, 229]. Robertson et al. investigated two target thresholds for CPP in patients with severe TBI, comparing 60 mmHg and 70 mmHg, and found that maintaining the higher threshold was associated with larger fluid volumes, worsening LI without improving overall patient outcomes [230]. These findings are in accordance with those of Lennihan et al., who, in a single-center study involving 82 patients, found that prophylactic hypervolemic therapy—consisting of colloids and crystalloids—had no effect on cerebral blood flow (CBF), vasospasm, or cerebral infarction compared to normovolemia [231]. In their investigation of delayed ischemic neurological deficit treatment, Ibrahim and

Macdonald observed that, among 123 patients, the use of colloids and a positive fluid balance were connected to less favorable outcomes [232]. Likewise, a separate study involving 288 patients also indicated that a positive fluid balance was associated with poorer functional outcomes [104].

Given the complexity of fluid management in patients with concomitant ARDS and ABI, a consensus reached during the ESICM LIVES2016 conference in October 2016, involving 22 international experts, emphasizes the importance of achieving normovolemia through a multimodal approach, guided by multiple hemodynamic variables. Arterial blood pressure and fluid balance should be the primary endpoints, while additional factors such as CO, $ScvO_2$, blood lactate, and urinary output may further optimize fluid therapy. The use of CVP alone is discouraged, and a restrictive fluid strategy targeting a negative fluid balance is not recommended. These approaches are essential to mitigating the risks of both hypervolemia and hypovolemia [227].

Fluid management in septic patients with ARDS

Sepsis is defined as organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is a more severe stage characterized by profound circulatory, cellular, and metabolic abnormalities, which significantly elevate the risk of mortality [233]. The diagnosis of septic shock is established when vasopressors are required to maintain a MAP of at least 65 mmHg, in conjunction with a lactate level greater than 2 mmol/L, despite adequate fluid resuscitation. As mentioned above, according to the most recent Surviving Sepsis Campaign guidelines, it is suggested that a fluid bolus of 30 mL/kg of intravenous crystalloid should be administered within the first 3 h of treatment. However, this recommendation is classified as "weak" as it is based on evidence of low quality [138]. The administration of intravenous fluids plays a crucial role in augmenting CO and blood pressure, preserving or increasing intravascular fluid volume, and facilitating the administration of therapeutic agents. However, while this follows the Frank–Starling mechanism, where increased preload enhances stroke volume in normal conditions, its effectiveness may be diminished in sepsis [124, 234].

LI is a common complication in patients with sepsis, often emerging as the earliest and most affected organ during the onset of multiple organ dysfunction. Research shows that 25–50% of individuals with sepsis develop LI, with associated mortality rates around 40% [235–237]. Although substantial research indicates that early goal-directed resuscitation improves outcomes in patients with septic shock and that conservative fluid management benefits those with LI, these two strategies may seem contradictory [22]. Indeed, inappropriate fluid resuscitation may exacerbate shock by significantly elevating filling pressures, which can exceed the compensatory capabilities of the heart as the patient approaches the plateau of the Frank–Starling curve [234]. Furthermore, although intravenous fluid boluses temporarily increase intravascular volume, they can ultimately cause pathological extravascular fluid leakage due to elevated left atrial pressure, leading to impaired cellular function in multiple organs, such as the kidneys, liver, heart, and lungs [238–242]. Moreover, administering additional volume in cases of sepsis may worsen shock in a compromised RV by exacerbating both pressure and volume overload. When volume overload becomes excessive, RV function can be impaired due to reduced contractility. This overload also causes the interventricular septum to shift leftward, which decreases LV filling. As a result, CO is further reduced, enhancing the risk of RV failure and overall hemodynamic instability [243, 244]. In addition, changes in capillary permeability and reduced oncotic pressure in septic patients can lead to edema development, even in the absence of an increase in effective circulating blood volume [97, 245]. Indeed, in conditions of severe inflammation, such as sepsis or septic shock, the release of inflammatory mediators progressively degrades the endothelial glycocalyx, disrupting capillary integrity and leading to fluid leakage [246].

Another important consideration for the management of septic patients is the development of AKI and oliguria, primarily caused by hypovolemia. However, it is noteworthy that many cases of AKI, particularly those occurring during systemic inflammation and sepsis, are not responsive to volume resuscitation [247]. Notably, in adult ICU patients with sepsis, a positive fluid balance after the first day is associated with an increased risk of AKI, with fluid overload not only increasing mortality but also serving as a negative predictor for renal function recovery [248, 249]. Fluid resuscitation, although it can restore normal renal arterial flow, may lead to disrupted microcirculatory flow in the renal cortex, creating hypoxic regions next to normoxic areas, which disrupt renal oxygen extraction and facilitate the generation of reactive oxygen species, further exacerbating kidney injury [250]. Moreover, fluids should be considered comparable to drugs, as they can have deleterious side effects, including cytokine activation, damage to the capillary glycocalyx, and reduced kidney efficiency in filtering excess fluid and nitrogenous waste [251].

Despite that liberal fluid strategy is a widely used approach during the initial resuscitation phase of septic shock management [20, 238, 252, 253], it has been increasingly questioned recently, as hemodynamic uncoupling suggests that stabilizing cardiovascular

parameters does not always enhance microcirculatory perfusion, and aggressive treatments may further aggravate glycocalyx damage and endothelial dysfunction [254]. The recommended fluid volume has been widely debated in recent years, as patients in modern early EGDT and usual care trials received a median of 27 mL/kg of fluid before randomization, leading to the conclusion that treatment should be individualized, focusing on "glycocalyx resuscitation" based on fluid tolerance and fluid responsiveness [255–257]. This approach could be meaningful, as a recent large, multicenter randomized trial (CLOVERS, NCT03434028) highlighted that in patients with sepsis-induced hypotension unresponsive to 1–3 L of intravenous fluid, a restrictive fluid strategy with earlier vasopressor use showed no significant impact on mortality before discharge home by day 90 compared to a liberal fluid strategy [258].

As previously noted, the "salvage, optimization, stabilization, de-escalation" strategy is proposed as a general framework for fluid resuscitation, emphasizing that fluid administration should be adjusted based on the disease's progression. During the initial salvage phase, generous administration of lifesaving fluids is essential. Once hemodynamic monitoring is accessible, fluid administration should be adjusted based on the patient's fluid status and the assessment of any further fluid requirements (Fig. 2) [97]. Perner et al. proposed a personalized fluid management strategy, which involves the administration of repeated 250–500 mL intravenous crystalloid boluses, continuous monitoring of fluid responsiveness, and the early use of vasopressors if circulation does not improve [259]. If hemodynamic stability is achieved or the patient no longer responds, aggressive fluid administration should be stopped [260]. Once permanent hemodynamic stability is established during the de-escalation phase, managing fluid balance may involve the use of diuresis or, in cases, where diuresis is ineffective, RRT [261]. Indeed, while diuretics may be beneficial in ICU patients with excess fluid and AKI by promoting a negative fluid balance, their effectiveness can be limited by delays in initiation, improper dosing, and concerns about side effects, such as AKI, often making RRT necessary [247, 262].

Future directions

Despite advances in fluid management for patients with ARDS, the optimal choice of fluids across the various phases of resuscitation remains unclear [136]. In addition, the role of combining different fluids, such as crystalloids and colloids, in specific clinical contexts is still unresolved [97]. Particularly for HAS, further research is needed to assess the effects of different concentrations, especially in patients with sepsis and ABI. In brain-injured patients, attention should be given to the tonicity of albumin solutions, and potential benefits of hypertonic 20–25% HAS should be explored, as existing data from the SAFE–TBI study demonstrated increased mortality in TBI patients who received 4% HAS [21, 263]. Moreover, existing data on the use of albumin or balanced crystalloids in patients with ARDS, particularly regarding patient-centered and long-term outcomes, are limited and warrant further investigation [164]. Finally, due to the uncertainty of evidence regarding fluid strategies in patients with concomitant circulatory failure and ARDS, future research considering ARDS sub-phenotypes is needed [264].

Conclusions

The destruction of endothelial and epithelial barriers and inflammatory cascades is a major contributor to the pathophysiology of ARDS. Hypervolemia is commonly present in patients with ARDS, making fluid management a cornerstone of therapeutic strategies, especially in the context of concurrent shock, as seen in septic patients and patients with ABI. The "salvage, optimization, stabilization, de-escalation" concept is the recommended strategy for fluid resuscitation, where the initial intensive fluid administration is followed by a restrictive fluid strategy, including diuretics and RRT, once hemodynamic stability has been achieved. Nonetheless, future research investigating fluid management in patients with concomitant ARDS and circulatory failure, considering ARDS sub-phenotypes, is urgently needed.

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